PTO/SB/21 (09-04)

# TRANSMITTAL FORM

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| Application Number | 09/825,242 |
| Filing Date | April 2, 2001 |
| First Named Inventor | Eisenberg, Stephen P. |
| Art Unit | 1631 |
| Examiner Name | John Brusca |
| Attorney Docket Number | 019496-001810US |

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## ENCLOSURES *(Check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
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  - Return Postcard
  - Appeal Brief submitted in triplicate

**Remarks** The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Townsend and Townsend and Crew LLP | | |
| Signature | J. Liebeschuetz | | |
| Printed name | Joe Liebeschuetz | | |
| Date | March 9, 2005 | Reg. No. | 37,505 |

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60440281 v1

*Effective on 12/08/2004.*
*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*

# FEE TRANSMITTAL
## For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

| TOTAL AMOUNT OF PAYMENT | ($) 500 |
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| Complete if Known | |
|---|---|
| Application Number | 09/825,242 |
| Filing Date | April 2, 2001 |
| First Named Inventor | Eisenberg, Stephen P. |
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| Art Unit | 1631 |
| Attorney Docket No. | 019496-001810US |

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**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

| Application Type | FILING FEES Fee ($) | FILING FEES Small Entity Fee ($) | SEARCH FEES Fee ($) | SEARCH FEES Small Entity Fee ($) | EXAMINATION FEES Fee ($) | EXAMINATION FEES Small Entity Fee ($) | Fees Paid ($) |
|---|---|---|---|---|---|---|---|
| Utility | 300 | 150 | 500 | 250 | 200 | 100 | |
| Design | 200 | 100 | 100 | 50 | 130 | 65 | |
| Plant | 200 | 100 | 300 | 150 | 160 | 80 | |
| Reissue | 300 | 150 | 500 | 250 | 600 | 300 | |
| Provisional | 200 | 100 | 0 | 0 | 0 | 0 | |

**2. EXCESS CLAIM FEES**

| Fee Description | Fee ($) | Small Entity Fee ($) |
|---|---|---|
| Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent | 50 | 25 |
| Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent | 200 | 100 |
| Multiple dependent claims | 360 | 180 |

| Total Claims | Extra Claims | Fee ($) | Fee Paid ($) |
|---|---|---|---|
| _____ | -20 or HP = _____ | x _____ | = _____ |

HP = highest number of total claims paid for, if greater than 20

| Indep. Claims | Extra Claims | Fee ($) | Fee Paid ($) |
|---|---|---|---|
| _____ | -3 or HP = _____ | x _____ | = _____ |

HP = highest number of independent claims paid for, if greater than 3

| Multiple Dependent Claims Fee ($) | Multiple Dependent Claims Fee Paid ($) |
|---|---|
| _____ | _____ |

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| Total Sheets | Extra Sheets | Number of each additional 50 or fraction thereof | Fee ($) | Fee Paid ($) |
|---|---|---|---|---|
| _____ - 100 = | _____ / 50 = | _____ (round **up** to a whole number) | x _____ | = _____ |

**4. OTHER FEE(S)**

| | Fees Paid ($) |
|---|---|
| Non-English Specification, $130 fee (no small entity discount) | _____ |
| **Other: Filing a brief in support of an appeal** | 500 |

**SUBMITTED BY**

| Signature | J. Liebeschuetz | Registration No. (Attorney/Agent) 37,505 | Telephone 650-326-2400 |
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| Name (Print/Type) | Joe Liebeschuetz | | Date March 9, 2005 |

60440321 v1

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On March 9, 2005

TOWNSEND and TOWNSEND and CREW LLP

By: Brenda J. Dolly



PATENT
Attorney Docket No.: 019496-001810US
Client Ref. No. S1-US2

Zinc
AF
1631

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re application of:

EISENBERG et al.

Application No.: 09/825,242

Filed: April 2, 2001

For: SELECTION OF SITES FOR TARGETING BY ZINC FINGER PROTEINS AND METHODS OF DESIGNING ZINC FINGER PROTEINS TO BIND TO PRESELECTED SITES

Examiner: John S. Brusca

Art Unit: 1631

**APPELLANTS' BRIEF UNDER 37 CFR § 1.192**

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed on January 6, 2005 for the above-referenced application, Appellants submit this Brief on Appeal. This Brief is submitted in triplicate as required under 37 CFR § 1.192.



# APPEAL BRIEF

# TABLE OF CONTENTS

## 1. REAL PARTY IN INTEREST

Sangamo Biosciences, Inc.

## 2. RELATED APPEALS AND INTERFERENCES

None

## 3. STATUS OF CLAIMS

Claims 35, 37, 38, 40-43, 48, 49, 52 and 53 are pending. Claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 are rejected and appealed. Claims 41 and 52 are objected to as depending from an unallowable claim. Claims 1-34, 26, 39, 44-47, 50, and 51 are cancelled.

## 4. STATUS OF AMENDMENTS

A response to final rejection was filed December 6, 2004 and was considered. However, no amendments were made to either the claims or specification. No amendments have been filed subsequently.

## 5. SUMMARY OF CLAIMED SUBJECT MATTER

The presently claimed invention is directed to methods of designing, and optionally producing, a zinc finger protein capable of binding a preselected target site using information from a database of precharacterized zinc finger proteins (see, e.g., specification at pp. 29-33). However, the claims do not merely recite using a database to design a zinc finger protein, but rather recite several distinct steps by which this process is accomplished. The process as defined by claim 35 starts with a database storing information regarding the amino acid sequences of fingers from zinc finger proteins and their corresponding nucleotide target sequences. Specifically, step (a) of claim 35 requires that the database comprise designations for a plurality of zinc finger proteins, and subdesignations for each of three fingers for each zinc finger protein (see, e.g., p. 30, lines 13-33). The database also contains a corresponding nucleic acid sequence for each zinc finger protein, the sequence comprising at least first, second and third triplets bounds by the first, second and third fingers respectively in each zinc finger protein (id.). Table 9 illustrates the organization of an exemplary database of the claimed invention (see p. 58). Step (b) of claim 35 requires providing a preselected target site for design of a zinc finger protein (see, e.g., p. 31, lines 1-2). Whereas the

nucleic acid sequences referred to in step (a) are the sequences bound by the precharacterized proteins in the database, the target site in step (b) is the sequence to be bound by a zinc finger protein that is designed by the claimed method. The method searches through the database (step (c)) to find zinc finger proteins, each of which comprises a finger that bind to at least one triplet of the target site recited in step (b), organizing such zinc finger proteins in subsets according to which triplet they bind (see, e.g., p. 31, lines 7-18). The method then outputs designations and subdesignations of the zinc finger proteins in the sets identified in step (c) (see, e.g., p. 31, lines 20-23. Finally, in step (e), a zinc finger protein or a nucleic acid encoding the same is produced (see, e.g., paragraph bridging pp. 31-32 and pp. 33-36).

Independent claim 37 is directed to a method similar to that of claim 35 except that claim 37 requires a step of identifying subsets of zinc finger protein(s) based on both the binding specificity of a zinc finger and the position in the protein from which the zinc finger binds its triplet subsite (step (d)) (see, e.g., p. 31, lines 10-12). As noted in the specification (see, e.g., p. 29, lines 26-30), such is advantageous because when the environment of each finger in a designed zinc finger protein is analogous to its environment in the precharacterized zinc finger protein in the database, it is likely to bind with similar specificity and affinity in the designed zinc finger protein as it did in the precharacterized protein.

Independent claims 42 and 43 are directed to methods similar to that of claim 37, except that claims 42 and 43 specify that the precharacterized zinc finger proteins in the database comprise first and second fingers (see, e.g., paragraph bridging pp. 32-33). Claim 42 specifies that the first and second fingers of the designed zinc finger protein are provided by zinc fingers occupying first and second positions in zinc finger proteins in the database. Claim 43 specifies that first and third fingers of a designed finger protein are provided by zinc fingers occupying the first and second positions of precharacterized zinc finger proteins in the database (p. 32, line 33 to p. 33, line 3).

Independent claims 48, 49 and 53 are respectively directed to a computer program product, a system and a computer-implemented method for implementation of design methods of the type specified in claim 35 (see, e.g., p. 41, line 9 to p. 43, line 14).

## 6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 35, 40, 48, 49 and 53 would have been obvious under 35 USC 103 over Choo, Nature 372, 642-645 (1994) [Choo (1994b)], in view of Choo, Proc. Natl. Acad. Sci.

USA 91, 11163-11167 (1994) [Choo (1994a)] in view of Corbi, FEBS Lett. 417, 71-74 (1997) [Corbi].

2. Whether claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 would have been obvious under 35 USC 103 over Choo (1994b) in view of Choo (1994a) in further view of Isalan, Biochem. 37, 12026-12033 (1998) [Isalan].

## 7. ARGUMENT

### 7.1 Claims 35, 40, 48, 49 and 53 Not Obvious over Choo (1994b), in view of Choo (1994a) in view of Corbi

#### 7.1.1 The Examiner's Rationale

The Examiner's rationale is stated in the final office action mailed October 7, 2004. Choo (1994b) is cited as discussing a method of designing a zinc finger protein that binds to a BCR-ABL target site. The Examiner acknowledges that Choo (1994b) does not explicitly show three finger zinc finger proteins, computer-based methods or a database in which zinc finger proteins have a third finger different from at least one third finger of another protein in the database (final office action at p. 4). Choo (1994a) is cited as disclosing screening a phage display library in which middle finger of a three-finger protein is randomized (final office action at p. 5, first paragraph). Corbi is cited as disclosing a zinc finger protein termed Mago (Figs. 1-2), and a target binding site (Fig. 3). The third finger of Corbi's protein is said to be different from that of Choo (1994b) (final office action at p. 5, second paragraph). The Examiner takes the view that it would have been obvious to precharacterize the selected random library members of Choo (1994b) and to record such characterizations in a database as allegedly shown in Choo (1994a) Fig. 2 (final office action at p. 5, 3rd paragraph). The Examiner also takes the view that it would have been obvious to automate the generation and use of the database by use of computers because it is obvious to automate a process (final office action at p. 5, 3rd paragraph). The Examiner further alleges it would have been obvious to add further zinc finger proteins such as the Mago protein of Corbi[1] to increase further the diversity

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[1] Although the Office Action does not state what the protein of Corbi would be added to, Appellants assume that the Examiner is suggesting that it would have been obvious to add the *protein* disclosed by Corbi. to the database of *zinc* fingers allegedly disclosed by Choo (1994a)

of choices because zinc finger proteins designed in Choo (1994b) had variability in their affinity and subsequent screening was required (final office action, sentence bridging pp. 5-6).

### 7.1.2 The Cited References

Choo (1994b) discusses an experiment to design a zinc finger protein to bind to a single preselected target sequence (5'GCA GAA GCC3') which contains the BCR-ABL junction. Fig. 2 of Choo (1994b) (which appellants understand the Examiner considers to be a database) tabulates the amino acid sequences of several individual fingers together with which triplet position in the target site is bound by the finger. Choo (1994b) indicates that these fingers were selected by the method of Choo (1994a).

Choo (1994a) discusses a method of selecting a zinc finger protein in which a randomized middle figure is flanked by first and third constant fingers from the natural protein Zif268. The first and third constant fingers bind to the respective triplets in the natural Zif268 target site (5'GCG TGG GCG3') and thus are not relevant to Choo (1994b)'s goal of designing a zinc finger protein to bind to the target site 5'GCA GAA GCC3'. Figure 2 of Choo (1994a) (which appellants understand the Examiner considers to be a database) lists amino acid sequences of selected middle fingers of a zinc finger protein together with triplets bound by the fingers. From the data summarized in this Figure, Choo (1994a) infers that amino acid positions -1, +3, +6 and +2 are involved in recognition of DNA (see p. 11166, second column, 4th paragraph).

Corbi discusses the design of a zinc finger protein termed Mago to bind the target sequence 5' ATG TGG GTT 3' (p. 72, second column first paragraph). The design was based on a syllabic code relating amino acids in a zinc finger to nucleotides in a DNA triplet (id.)

### 7.1.3 Analysis

(a) Non-Disclosed Claim Elements

The prior art references when combined must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Here, even assuming *arguendo* that the cited references are properly combined, the references neither individually or in

combination provide any disclosure of a database comprising designations for a plurality of three-finger zinc finger proteins, subdesignations for each of three fingers for each zinc finger protein, and their corresponding target nucleic acid sequences, as specified in claim 35, 50, 48, 49 and 53. The tables shown in Figs. 2 of the respective Choo references suffer from similar deficiencies in that both provide designations for only a single finger of a multi-finger zinc finger protein and neither presents a target sequence with three triplets. Although the physical zinc finger proteins, from which the information discussed in the cited references was obtained, may inherently have had three zinc fingers, these physical proteins are not components of a database. If Fig. 2 of either Choo reference is viewed as a database, then the database is composed of the typewritten data in the tables. These typewritten data do not expressly or inherently contain designations of zinc finger proteins, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed. Corbi does nothing to compensate for the deficiencies of Choo (1994a) and (1994b) in this regard.

Because the combination of references does not teach a database comprising designations of multi-finger zinc finger proteins and subdesignations of each of three fingers for each zinc finger protein, it follows that the combination of reference sequences also does not disclose claim 35 step (c) of identifying first, second and thirds sets of zinc finger proteins in the database. Similarly, the combination of references does not teach claim 35 step (d) of outputting designations and subdesignations of the zinc finger proteins.

In the advisory action, the Examiner denies having acknowledged that Choo (1994b) does not show three finger zinc finger proteins (first paragraph of continuation sheet). In response, appellants were referring to the Examiner's remark "Choo et al. (1994b) does not explicitly show that the randomized library of zinc finger proteins consists of three finger zinc finger proteins..." (final office action at p. 4). Further, the Examiner has not addressed the substance of appellants' position that although the physical zinc finger proteins, from which the information described in the cited references was obtained, may inherently have had three zinc fingers, these physical proteins are not components of a database. To reiterate, the typewritten data of Fig. 2 in either Choo reference do

not expressly or inherently contain designations of zinc finger *proteins* comprising at least three zinc fingers, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed.

In the advisory action, the Examiner also alleges that it would have been obvious to list the sequences of all three fingers of each zinc finger protein analyzed in the library of Choo (1994a) to provide a complete description of each zinc finger protein and to facilitate comparison to other zinc finger proteins (third paragraph of continuation sheet). However, the Examiner appears to overlook that Choo (1994a) is a secondary reference in the rejection, which does not itself provide any relevant discussion of designing zinc finger proteins. The secondary reference would be relevant only insofar as it suggested modifying the design of the alleged database of the primary reference Choo (1994b). Thus, the issue is not whether it would have been obvious to modify the teaching of Choo (1994a) for some purpose unrelated to Choo (1994b) and not disclosed in either reference, but whether Choo(1994a) suggested modifying Choo (1994b). In both Choo (1994a) and (1994b), the single fingers listed in the respective Fig. 2's of the references were selected as a randomized middle figure flanked by constant first and third fingers from the natural protein Zif268. The first and third constant fingers bind to the respective triplets in the natural Zif268 target site (5'GCG TGG GCG3') and thus are not relevant to Choo (1994b)'s goal of designing a zinc finger protein to bind to the target site 5'GCA GAA GCC3'. Thus, even if is assumed *arguendo* there might be some purpose unrelated to Choo (1994b) for which one would want to list the constant first and second fingers in Figure 2 of Choo (1994a), such an unrelated purpose would not have motivated one to include the constant first and third fingers in Fig. 2 of Choo (1994b).

For these reasons, it is respectfully submitted that the combination of references does not disclose a database comprising designations for a plurality of multi-finger zinc finger proteins, subdesignations for each of three fingers for each zinc finger protein, and their corresponding target nucleic acid sequences, or a step of identifying first, second and third sets of zinc finger proteins in the database, or a step of outputting designations and subdesignations of the zinc finger proteins.

(b) No Motivation to Combine

To support combination of references, motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). "Actual evidence" of "clear and particular" motivation is required. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "[T]here must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied).

Here, the Examiner's proposed motivation of increasing diversity of choices would not have motivated combination of Corbi with Choo (1994b). The goal of Choo (1994b), as the Examiner recognizes, was to design a zinc finger protein to a specific target sequence that spans the Bcr-Abl junction (i.e., (5'GCA GAA GCC3'). By contrast, Corbi's protein was designed to bind to the target ATG TGG GTT (see Fig. 3 of Corbi). There is no apparent similarity between Corbi's target and that of Choo (1994b). Therefore, the zinc finger components of Corbi's zinc finger protein would not bind to the triplets of Choo (1994b), and would be of no apparent use in Choo (1994b)'s goal of designing a zinc finger protein to bind to the Bcr-Abl target. No other goal is disclosed or suggested by Choo (1994b).

In the advisory action, the Examiner disagrees with appellants' position on the basis that it would have been obvious to add any and all data of known zinc finger proteins to the database of Choo (1994a) to allow selection of zinc fingers with specificity for any desired target site. In response, the alleged database of Choo (1994a) summarizes results from a particular experiment, and it would not be usual scientific practice to merge data from a particular experiment with data from any and all known zinc finger proteins regardless of how the data were obtained. Moreover, the Examiner again appears to overlook that Choo (1994a) is cited as a secondary reference to modify the teachings of Choo (1994b). Even if it is assumed *arguendo* one might want to modify Fig. 2 of Choo (1994a) to include data from additional zinc finger proteins albeit for a purpose not specified in the reference, this does not mean one would want similarly to modify the database of Choo (1994b) to include Corbi's protein. To reiterate, Corbi's zinc finger protein would not bind to the

triplets of Choo (1994b), and would be of no apparent use in Choo (1994b)'s goal of designing a zinc finger protein to bind to the Bcr-Abl target. No other goal is disclosed or suggested by Choo (1994b).

Claims 48, 49 and 53 are distinguished on additional grounds. The Examiner's allegation that automation of a process by use of a computer is obvious assumes the references disclose a procedure capable of being automated. In Choo (1994b), the goal was to design a zinc finger protein to a specific target sequence and every sequence in Fig. 2 was already known to bind to one of the triplets in that target sequence. Fig. 2 already indicates which sequences bind to which triplet of the intended target sequence. It is not apparent how any processing of the data in a computer could make the data in Fig. 2 any clearer or more useful for designing a zinc finger protein to bind to Choo(1994b)'s intended target sequence. Thus, it would not have been obvious to use a computer to process the data in Fig. 2 of Choo 1994(b) particularly according to the steps required by claims 48, 49 and 53. Likewise, Choo (1994a) does not disclose any use of the data in Fig. 2 susceptible to automation. Fig. 2 is merely a compilation of data obtained from a particular experiment. Without identification of a process that could benefit from computerized automation, it would not have been obvious to employ a computer, as claimed.

The Examiner disagrees with appellants' position on the basis that it is obvious to automate analysis of a database by the use of computers to store data and display and search the data to facilitate analysis of large databases (advisory action, continuation sheet, at paragraph 5). The Examiner notes that Choo (1994a) discusses screening a library of $2.6 \times 10^6$ members, which could be entered into his database (advisory action at paragraph (4)). However, Choo (1994a) did not analyze the entire library, but only a small portion of it returned by selection, the results from which are shown in Fig. 2. The majority of library members were not characterized for encoded sequence or target binding specificity, and thus could not have been entered into a database, much less analyzed. Moreover, the Examiner is overlooking that Choo (1994a) is cited as a secondary reference. Even if it is assumed *arguendo* that it were obvious to use a computer to analyze the data of Choo (1994a) for some purpose (albeit not disclosed in the reference) this does not mean that it

would have been obvious to use a computer to automate the design of a protein from the data in Fig. 2 of Choo (1994b) according to the specific steps of claims 48, 49 and 53.

The Examiner also states that it would have been obvious to add other zinc finger proteins with a wide diversity of specificities and alternative structures for use in the method of Choo (1994b) (advisory action, continuation sheet, paragraph 5). In fact, a wide diversity of specificities, insofar as different from the intended target sequence, would not be useful in Choo (1994b)'s goal of designing a zinc finger protein to bind to the Bcr-Abl target. Moreover, even if one added alternative finger sequences to Fig. 2 of Choo (1994b) having the same specificities, it would not have been obvious to use a computer in the design process as claimed. In the absence of motivation to do otherwise, such additional fingers would be represented in the same manner as the other sequences in Fig. 2 of Choo (1994b). Fig. 2 of Choo (1994b) already indicates which fingers bind to which triplets of the intended target sequences. As discussed above, it is not apparent how using a computer according to the claimed method steps would assist in a design process starting from Fig. 2 of Choo (1994b).

For these reasons, it is submitted that a prima facie case of obviousness has not been established and the rejection should be reversed.

**7.2 Claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 Not Obvious over Choo (1994b) in view of Choo (1994a) in further view of Isalan**

**7.2.1 The Examiner's Rationale**

The Examiner's position is stated in the final office action at pp. 6-8. Choo (1994a) and Choo (1994b) are cited as above. Isalan is cited as showing two variants of zinc finger libraries of Choo (1994a) in which the second and third fingers contain variant sequences. The Examiner alleges that the target binding site of the library members is shown in Fig. 3 of Isalan. The Examiner also alleges that Isalan shows that the context of neighboring fingers affects the target site specificity of a zinc finger. The Examiner takes the view that it would have been obvious to precharacterize the selected random library members of Choo (1994b) to any desired extent, and to record such characterizations in a database as allegedly shown in Choo (1994a). The Examiner also alleges it

would have been obvious to use computers because it is obvious to automate a process. The Examiner further alleges it would have been obvious to use libraries in which multiple fingers including the third finger were randomized so that zinc finger neighbor context was varied in view of Isalan's teaching that randomization of neighboring fingers allows for increased diversity of binding site specificity in individual zinc fingers. The Examiner also alleges that it would have been obvious to maintain correspondence between zinc finger positions in a database of zinc finger proteins and the position of the zinc finger in a designed zinc finger protein because Isalan shows that the identity of neighboring zinc fingers affects the specificity of a zinc finger.

### 7.2.2 The Cited Reference

Isalan reports that binding specificity of zinc fingers is affected by interactions between neighboring zinc fingers (see p. 13026, second column second paragraph). Islan notes that such interactions have limited the range of specificities that have been previously isolated (see abstract). Isalan proposes the limitation can be overcome by a strategy of co-randomizing adjacent fingers (see Abstract).

### 7.2.3 Analysis

(a) Non-Disclosed Claim Elements

The previous comments regarding the combination of Choo (1994b) with Choo (1994a) not resulting in a database comprising designations for a plurality of zinc finger proteins, subdesignations for each of the fingers of each zinc finger protein, and a corresponding target nucleic acid sequences for each zinc finger protein in the database are equally applicable to the above rejection. So too are the previous comments regarding lack of disclosure of a step of identifying first, second and thirds sets of zinc finger proteins in the database, or a step of outputting designations and subdesignations of the zinc finger proteins. As noted, insofar as Figs. 2 of Choo (1994b) and (1994a) are regarded as being databases, they are databases of only single zinc fingers, not databases of multi-finger zinc finger proteins as claimed. Fig. 3 of Isalan shows amino acid

sequence for only one and a fraction fingers, and target sequences of only two nucleotides. Although the physical zinc finger proteins from which the information described in the cited references was obtained may inherently have had three zinc fingers and the target sequence may have had three triplets, these physical proteins and target sequence are not components of a database. If Fig. 2 of either Choo reference or Fig. 3 of Isalan is viewed as a database, then the database is composed of the typewritten data in the Figures. These typewritten data do not expressly or inherently contain designations of multi-finger zinc finger proteins, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed.

(b) No Motivation to Combine

The Examiner's proposed motivation of increasing diversity of choices would not have motivated combination of Isalan with Choo (1994b). The goal of Choo (1994b) was to design a zinc finger protein to a specific target sequence that spans the Bcr-Abl junction (i.e., (5'GCA GAA GCC3'). By contrast, the zinc finger proteins of Isalan were selected to bind to target sequences of the form 5'GNX XCG GCG 3' or 5' GCX XCG GCG 3'. At most, only the third finger of some of Isalan's proteins would bind to a triplet present in Choo (1994b)'s target sequence (i.e., GCX or GNX). However, Isalan's selection strategy was to co-randomize and select the third and second fingers simultaneously. Thus, Isalan's third fingers were always co-selected with neighboring second fingers that would not have the appropriate specificity to bind to Choo (1994b)'s target sequence. One would not have been motivated to separate Isalan's third fingers from the neighboring second fingers with which they were co-selected because to do so would effectively nullify the purpose of the co-selection. One also could not use a combination of Isalan's third and second fingers together with Choo (1994b) fingers, because the second fingers of Isalan have the wrong target specificity. Therefore, one would not have been motivated to combine Isalan's third fingers with the other zinc fingers shown in Fig. 2 of Choo (1994b).

Claims 37, 42 and 43, the references are distinguished for an additional reason, namely, Isalan would not have motivated a design method which uses information on the position of the zinc fingers in the precharacterized zinc finger proteins in the database. Specifically, claim 37

requires a step of identifying subsets of zinc finger protein(s) based on both the binding specificity of a zinc finger and the position in the protein from which the zinc finger binds its triplet subsite. As noted in the specification (see, e.g., p. 29, lines 26-30), such is advantageous because when the environment of each finger in a designed zinc finger protein is analogous to its environment in the precharacterized zinc finger protein in the database, it is likely to bind with similar specificity and affinity in the designed zinc finger protein as it did in the precharacterized protein.

Isalan's observation that the binding specificity of one zinc finger in a zinc finger protein may depend on the identity of its neighboring fingers would not have suggested the claimed methods. Rather, the observation suggests that the artisan do what Isalan himself did to overcome the problem of neighboring fingers, that is randomize and select more than one finger simultaneously:

> [W]e now show that this limitation can be overcome by the concerted randomization of certain amino acid positions in adjacent zinc fingers that specify overlapping DNA subsites. This illustrates an important mechanism underlying DNA recognition by arrays of zinc fingers, and points the way to improved strategies for the design of highly specific zinc finger proteins that bind any given nucleotide sequence.
>
> Isalan, at p. 12026 (Abstract)

By teaching the importance of selecting neighboring fingers simultaneously, Isalan effectively teaches away from the claimed methods which result in assembly of individual fingers in a modular fashion without regard to whether the fingers previously existed as neighbors. The presently claimed methods do not seek to preserve sequence context by maintaining a zinc finger in contact with its neighboring zinc finger in a preexisting zinc finger protein (as in Isalan's solution) but rather to preserve positional context by placing a zinc finger in a designed protein in same position as it occurs in a preexisting protein. Isalan provides no indication that preservation of positional context without sequence context would be beneficial to zinc finger binding specificity. Without such an understanding, the artisan would not have been motivated to combine the teaching of Choo (1994a) and/or (1994b) with Isalan, much less in a way that approximates to the presently

claimed methods. Rather, the artisan would have simply done what Isalan did, namely co-randomize adjacent fingers.

In the advisory action, the Examiner indicates disagreement with appellants' position on the basis that Islan teaches interactions between neighboring fingers, and that selecting pairs of fingers allows for design of zinc finger proteins with desired specificity. As should be clear from the above discussion, appellants do not dispute Isalan's comments in this regard. However, as Appellants have explained above, and in response to the final rejection, such teaching actually leads one away from the claimed invention.

Appellants' previous comments regarding lack of motivation to use a computer when no process susceptible to automation is disclosed are also equally applicable to the present rejection of claims 48, 49 and 53. Figure 3 of Isalan like Fig. 2 of Choo (1994a) is merely a compilation of experimental data. Neither reference discloses any use of the data susceptible to automation. Further, it is not apparent how a computer could process the data of Fig. 2 of Choo (1994b), as discussed above. In the absence of a process susceptible to automation, it was not obvious to use a computer. Thus, claims 48, 49 and 53 are distinguished on additional grounds.

Claim 43 is distinguished on additional grounds in that it specifies a method of producing a zinc finger protein (or nucleic acid encoding the same) comprising first, second and third fingers using information from a database of zinc finger proteins comprising first and second fingers. The first and third fingers in the designed zinc finger protein are obtained from fingers occupying the first and second positions respectively in zinc finger proteins in the database. Such methods change the positional context of one of the fingers between the designed protein and the protein from which it was obtained in the database. Isalan teaches away from such methods.

## 8. CONCLUSION

For the reasons given above, it is respectfully submitted that the rejection should be reversed and remanded to the Examiner for allowance.

Respectfully submitted,

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## 9. CLAIM APPENDIX

**Claim 35.** A method of producing a zinc finger protein or a nucleic acid encoding the same, comprising:

(a) providing a database comprising designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, and subdesignations for each of the three fingers of each of the zinc finger proteins, wherein at least one protein in the database has a third finger that is different from the third finger of at least one other protein in the database; a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a preselected target site for design of a zinc finger protein, the target site comprising contiguous first, second and third triplets in a 3'-5' order,

(c) for the first, second and third triplet in the target site, identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) outputting designations and subdesignations of the zinc finger proteins in the first, second, and third sets identified in step (c); and

(e) producing (i) a zinc finger protein that binds to the target site comprising a first finger from a zinc finger protein from the first set, a second finger from a zinc finger protein from the second set, and a third finger from a zinc finger protein from the third set, or (ii) a nucleic acid encoding the zinc finger protein.

**Claim 37.** A method of producing a zinc finger protein or nucleic acid encoding the same comprising:

(a) providing a database comprising designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, and subdesignations for each of the three fingers of each of the zinc finger proteins;

a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a preselected target site for design of a zinc finger protein, the target site comprising contiguous first, second and third triplets in a 3'-5' order,

(c) for the first, second and third triplet in the target site, identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) identifying subsets of the first, second and third sets, the subset of the first set comprising zinc finger protein(s) comprising a finger that specifically binds to the first triplet in the target site from the first finger position of a zinc finger protein in the database; the subset of the second set comprising zinc finger protein(s) comprising a finger that specifically binds to the second triplet in the target site from the second finger position in a zinc finger protein in the database; the subset of the third set comprising zinc finger protein(s) comprising a finger that specifically binds to the third triplet in the target site from a third finger position in a zinc finger protein in the database;

(e) outputting designations and subdesignations of the subset of the first, second and third sets; and

(f) producing (i) a zinc finger protein comprising a first finger from the first subset, a second finger from the second subset, and a third finger from the third subset, or (ii) a nucleic acid encoding the same.

**Claim 38.** The method of claim 37, wherein the outputting comprises outputting the designations and subdesignations of the subsets of the first, second and third sets, and the first, second and third sets minus their respective subsets.

**Claim 40.** The method of claim 35, wherein the target site is provided by user input.

**Claim 41.** The method of claim 35 wherein the target site is provided by

providing a target nucleic acid to be targeted by a zinc finger protein;

selecting a plurality of potential target sites within the target nucleic acid sequence;

evaluating whether each selected target site comprises 5'NNx aNy bNzc3; and

outputting a selected target site within the target nucleic acid comprising 5'NNx aNy bNzc3', the output selected target site providing the target site in step (b) of claim 35, wherein

each of (x, a), (y, b) and (z, c) is (N, N) or (G, K);

at least one of (x, a), (y, b) and (z, c) is (G, K). and

N and K are IUPAC-IUB ambiguity codes.

**Claim 42.** A method of producing a zinc finger protein or a nucleic acid encoding the same, comprising:

(a) providing a database comprising

designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first and second fingers,

subdesignations for each of the fingers of each of the zinc finger proteins; and a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising first and second triplets specifically bound by the first and second fingers respectively, the triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first and second and fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a preselected target site for design of a ~~new~~ zinc finger protein, the target site comprising contiguous first and second triplets ordered 3'5' in the target site;

(c) for the first and second triplet in the target site, identifying first and second sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein comprising a finger specifically binding to the second triplet in the target site;

(d) identifying subsets of the first and second sets, the subset of the first set comprising zinc finger protein(s) comprising a finger that specifically binds to the first triplet in the target site from the first finger position of a zinc finger protein in the database; and the subset of the second set comprising zinc finger protein(s) comprising a finger that specifically binds to the second triplet in the target site from the second finger position in a zinc finger protein in the database;

(e) outputting designations and subdesignations of the zinc finger proteins in the subsets of the first, and second sets identified in step (c); and

(f) producing (i) a zinc finger protein that binds to the target site comprising a first finger from a zinc finger protein from the subset of the first set and a second finger from a zinc finger protein from a subset of the second set, or (ii) a nucleic acid encoding the same.

**Claim 43.** A method of producing a zinc finger protein or a nucleic acid encoding the same, comprising:

(a) providing a database comprising:

designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first and second fingers;

subdesignations for each of the fingers of each of the zinc finger proteins; and

a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising first, and second triplets specifically bound by the first and second fingers respectively, the triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first and second and fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a preselected target site for design of a zinc finger protein, the target site comprising contiguous first, second and third triplets ordered 3'5' in the target site;

(c) for the first and third triplet in the target site, identifying first and second sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) identifying subsets of the first and second sets, the subset of the first set comprising zinc finger protein(s) comprising a finger that specifically binds to the first triplet in the target site from the first finger position of a zinc finger protein in the database; and the subset of the second set comprising zinc finger protein(s) comprising a finger that specifically binds to the third triplet in the target site from the second finger position in a zinc finger protein in the database;

(e) outputting designations and subdesignations of the subsets of the zinc finger proteins in the first and second sets identified in step (c); and

(f) producing (i) a zinc finger protein that binds to the target site comprising first, second and third fingers, wherein the first finger is from a zinc finger protein from the subset of the first set and the third finger is from a zinc finger protein from the subset of the second set, or (ii) a nucleic acid encoding the same.

**Claim 48.** A computer program product for designing a zinc finger protein comprising:

(a) code for providing a database comprising

designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, wherein at least one protein in the database has a third finger that is different from the third finger of at least one other protein in the database;

subdesignations for each of the three fingers of each of the zinc finger proteins;

a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminus to C-terminus);

(b) code for providing a preselected target site for design of a zinc finger protein, the target site comprising at least first, second and third triplets,

(c) for the first, second and third triplet in the target site, code for identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) code for outputting designations and subdesignations of the zinc finger proteins in the first, second, and third sets identified in step (c).

(e) a computer readable storage medium for holding the codes.

**Claim 49.** A system for designing a zinc finger protein comprising:

(a) a memory;

(b) a system bus;

(c) a processor operatively disposed to:

(1) provide a database comprising

designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, and subdesignations for each of the three fingers of each of the zinc finger proteins; wherein at least one protein in the database has a third finger that is different from the third finger of at least one other protein in the database;

a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5')in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminus to C-terminus);

(2) provide or be provided with a preselected target site for design of a ~~new~~ zinc finger protein, the target site comprising at least first, second and third triplets,

(3) for the first, second and third triplet in the target site, identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(4) output designations and subdesignations of the zinc finger proteins in the first, second, and third sets identified in step (3).

**Claim 52.** The method of claim 35 wherein the target site is provided by

providing a polynucleotide sequence;

selecting a potential target site within the polynucleotide sequence; the potential target site comprising contiguous first, second and third triplets of bases at first, second and third positions in the potential target site;

determining a plurality of subscores by applying a correspondence regime between triplets and triplet position in a sequence of three contiguous triplets, wherein each triplet has first, second and third corresponding positions, and each combination of triplet and triplet position has a particular subscore

calculating a score for the potential target site by combining subscores for the first, second, and third triplets;

repeating the selecting, determining and calculating steps at least once on a further potential target site comprising first, second and third triplets at first, second and third positions of the further potential target site to determine a further score;

providing output of at least one potential target site with its score, the at least one output potential target site providing the preselected target site for step (b) in claim 35.

**Claim 53.** A computer implemented method of designing a zinc finger protein comprising:

(a) providing a database comprising designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, and subdesignations for each of the three fingers of each of the zinc finger proteins; wherein at least one third finger of the plurality of precharacterized zinc finger proteins is different from at least one other third finger; a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a target site for design of a zinc finger protein, the target site comprising contiguous first, second and third triplets in a 3'-5' order,

(c) for the first, second and third triplet in the target site, identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) outputting designations and subdesignations of the zinc finger proteins in the first, second, and third sets identified in step (c).

## 10. Evidence Appendix

None.

## 11. Related Proceedings Appendix

None.